Heritability of Thoracic Spine Curvature and Genetic Correlations With Other Spine Traits: The Framingham Study

HHS Public Access

Author manuscript

J Bone Miner Res. Author manuscript; available in PMC 2017 January 31.

Published in final edited form as:

J Bone Miner Res. 2016 December ; 31(12): 2077–2084. doi:10.1002/jbmr.2925.

Heritability of Thoracic Spine Curvature and Genetic Correlations With Other Spine Traits: The Framingham Study

Michelle S Yau[1,2], **Serkalem Demissie**[3], **Yanhua Zhou**[3], **Dennis E Anderson**[4,5], **Amanda L Lorbergs**[1,2], **Douglas P Kiel**[1,2], **Brett T Allaire**[5], **Laiji Yang**[1], **L Adrienne Cupples**[3,6], **Thomas G Travison**[1,2], **Mary L Bouxsein**[4,5], **David Karasik**[1,7], and **Elizabeth J Samelson**[1,2]

[1]Institute for Aging Research, Hebrew SeniorLife, Boston, MA, USA

[2]Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

[3]Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA

[4]Center for Advanced Orthopaedic Studies, Beth Israel Deaconess Medical Center, Boston, MA, USA

[5]Department of Orthopedic Surgery, Harvard Medical School, Boston, MA, USA

[6]National Heart Lung and Blood Institute Framingham Heart Study, Framingham, MA, USA

[7]Faculty of Medicine in the Galilee, Bar Ilan University, Safed, Israel

Abstract

Hyperkyphosis is a common spinal disorder in older adults, characterized by excessive forward curvature of the thoracic spine and adverse health outcomes. The etiology of hyperkyphosis has not been firmly established, but may be related to changes that occur with aging in the vertebrae, discs, joints, and muscles, which function as a unit to support the spine. Determining the contribution of genetics to thoracic spine curvature and the degree of genetic sharing among co-occurring measures of spine health may provide insight into the etiology of hyperkyphosis. The purpose of our study was to estimate heritability of thoracic spine curvature using T_4–T_{12} kyphosis (Cobb) angle and genetic correlations between thoracic spine curvature and vertebral fracture, intervertebral disc height narrowing, facet joint osteoarthritis (OA), lumbar spine volumetric bone mineral density (vBMD), and paraspinal muscle area and density, which were all assessed from computed tomography (CT) images. Participants included 2063 women and men in the second and third generation offspring of the original cohort of the Framingham Study. Heritability of kyphosis angle, adjusted for age, sex, and weight, was 54% (95% confidence interval [CI], 43% to 64%). We found moderate genetic correlations between kyphosis angle and paraspinal muscle area ($\hat{\rho}_G$, −0.46; 95% CI, −0.67 to −0.26), vertebral fracture ($\hat{\rho}_G$, 0.39; 95% CI, 0.18 to 0.61), vBMD ($\hat{\rho}_G$, −0.23; 95% CI, −0.41 to −0.04), and paraspinal muscle density ($\hat{\rho}_G$,−0.22; 95% CI, −0.48 to 0.03).

Address correspondence to: Michelle S Yau, PhD, MPH, Institute for Aging Research, Hebrew SeniorLife, 1200 Centre Street, Boston, MA 02131, USA. michelleyau@hsl.harvard.edu.

Disclosures

All authors state that they have no conflicts of interest.

Genetic correlations between kyphosis angle and disc height narrowing ($\hat{\rho}_G$, 0.17; 95% CI, −0.05 to 0.38) and facet joint OA ($\hat{\rho}_G$, 0.05; 95% CI, −0.15 to 0.24) were low. Thoracic spine curvature may be heritable and share genetic factors with other age-related spine traits including trunk muscle size, vertebral fracture, and bone mineral density.

Keywords

AGING; QCT; DISEASES AND DISORDERS RELATED TO BONE; GENETIC RESEARCH; EPIDEMIOLOGY

Introduction

Hyperkyphosis, or excessive anterior curvature of the thoracic spine, is a commonly recognized condition in older adults, ranging in prevalence from 20% to 40%.[1,2] Hyperkyphosis is associated with several adverse health outcomes, including reduced physical functioning[3–5] and mobility,[6] increased risk of falls,[7] decreased lung function,[8] and higher mortality.[2]

Studies have identified few risk factors for increased severity of thoracic spine curvature, assessed on radiographs by a kyphosis (Cobb) angle. Lifestyle characteristics, such as smoking, alcohol use, and low levels of physical activity, have not been associated with worsening thoracic spine curvature in older women.[9] However, aging-related changes in the anatomic structures of the spine, particularly loss of height in the vertebral bodies and intervertebral discs, have been consistently associated with thoracic spine curvature severity.[1,9] For example, women with vertebral fracture have a six-degree higher kyphosis angle and a two-degree increase in kyphosis angle over 15 years compared to those without vertebral fracture. Women with degenerative disc disease have a four-degree higher kyphosis angle than those who do not have disc disease. Yet vertebral fractures and degenerative disc disease explain as little as 12% of the variation in thoracic spine curvature.[9] To illustrate, only one-third of women and men in the Rancho Bernardo Study with kyphosis angle 56 degrees and greater had vertebral fractures.[10] The posterior facet (zygapophyseal) joints function interdependently with the anterior discs, comprising a three-joint complex, or spinal “motion segment.” However, the role of degenerative changes in the facet joints in thoracic spine curvature has not yet been reported. Finally, there is some evidence that muscle density[11] and size[12] contribute to thoracic spine curvature severity, and interventions to improve trunk muscle strength have reduced/improved thoracic spine curvature in older women.[13,14]

The role of genetics in the etiology of hyperkyphosis has received little attention. Parental history of dowager’s hump has been shown to be associated with greater kyphosis angle, suggesting there may be an inherited component to thoracic spine curvature.[9] A study of 110 monozygotic and 136 dizygotic female twins reported heritability of 61% (95% confidence interval [CI], 46% to 72%) for thoracic kyphosis.[15] However, there have been no studies of heritability of thoracic spine curvature in extended families, and none have included men.

We hypothesized that development of hyperkyphosis may involve shared biological processes among spine traits that may be genetically regulated. To test this hypothesis, we used CT scans to evaluate spine traits in two generations of families from the Framingham Heart Study, an ongoing, community-based study of older adults. The purpose of our study was to determine the heritability of thoracic spine curvature and quantify the extent of shared genetic variation between thoracic spine curvature and other spine traits, including vertebral fracture, bone mineral density, disc height narrowing, facet joint osteoarthritis (OA), and paraspinal muscle area and density.

Subjects and Methods

Participants

This study includes cohort members of the Framingham Multi-Detector Computed Tomography Study (MDCT), which enrolled the second and third generation cohorts (including spouses) of the original cohort of the Framingham Heart Study.[16–18] Participants with large numbers of family members in the Framingham Heart Study were invited to enroll in the MDCT Study. Exclusion criteria included pregnancy, weight greater than 320 pounds, and age less than 40 years for women and 35 years for men.[19,20] A first CT examination was performed in 2002–2005 and a second examination in 2008–2011. The current study is based on assessments of images from the second CT examination. The acquisition in the second CT examination covered a longer length of the spine than the first examination, allowing for evaluation of spine traits in both the thoracic and lumbar spine.[21] These assessments include kyphosis angle, vertebral fracture, disc height narrowing, facet joint OA, and muscle density and area. However, information on volumetric BMD (vBMD) at the lumbar spine was available only from the first CT images acquired in 2002–2005.[21] The current study included 2063 individuals (aged 37 to 90 years) who had CT images evaluable for kyphosis assessment and attended corresponding study visits for assessment of clinical factors. These study visits occurred in 2005–2008 (cycle 8) for the second generation cohort, and in 2008–2011 (cycle 2) for the third generation cohort. Evaluation of vertebral fracture, disc height narrowing, and facet joint OA was restricted to individuals age 50 years and greater, so analysis of these phenotypes included a subset of 1172 participants.

Participants provided informed consent and the study was approved by institutional review boards at Boston University and Hebrew SeniorLife.

CT acquisition

CT images acquired from 2008 to 2011 were performed with a 64-section multidetector CT unit (Discovery VCT; General Electric Medical Systems, Milwaukee, WI, USA), which used a tube voltage of 120 kVp, tube current of 300/350 mA (≤220/>220 lb body weight), and gantry rotation of 350 ms. The thoracic acquisition covered the entire chest during a single inspirational breath hold and typically corresponds to T_4 to L_1 vertebral levels (slice thickness 0.625 mm, field of view [FOV] 35 cm). The abdominal acquisition began at the L_5/S_1 junction and 60 contiguous CT slices (slice thickness 2.5 mm, FOV 35 cm) were obtained above this point. The CT images acquired in 2008–2011 were used to evaluate kyphosis angle, vertebral fracture, disc height narrowing, facet joint OA, and trunk muscle

density and size. However, vBMD at the lumbar spine was measured from CT images acquired in 2002–2005.[21]

Kyphosis angle

Two operators were trained according to a standardized protocol to measure kyphosis (Cobb) angle, in degrees, from CT scout images using a semiautomated quantitative algorithm (SpineAnalyzer; Optasia Medical Ltd., Cheadle, UK). The algorithm provided standard six-point morphometry, as well as detailed annotation to define the shape of the vertebrae (Fig. 1).[22] Based on manual placement of points in the approximate center of the T_4 to L_4 vertebrae, the algorithm identified vertebral body margins, drew contours, and placed points for six-point morphometry. Point placements were adjusted as necessary by the operators. If one or both endplates could not be reliably contoured due to ribs, image quality, or metal artifacts, affected vertebrae were excluded from analysis. We calculated thoracic kyphosis angle, in degrees, as the angle between the superior endplate of T_4 and the inferior endplate of T_{12}. Greater kyphosis angle indicates worse, or more severe, forward curvature of the thoracic spine.

To test reliability, two operators repeated measurements of kyphosis angle on the scans of 20 participants on two occasions within a minimum of 2 weeks apart. We calculated intraclass coefficients to obtain interreader correlation, which was 0.97, and intrareader correlation, which was 0.98.

Vertebral fracture, disc height narrowing, and facet joint OA

A single, trained musculoskeletal radiologist used standardized protocols to evaluate presence and severity of three traits, prevalent vertebral fracture, disc height narrowing, and facet joint OA, at each spinal level from T_4 to L_4. The reader assigned a semiquantitative (SQ) score for each trait: SQ0 = none, SQ1 = mild, SQ2 = moderate, and SQ3 = severe. To evaluate intrareader reliability, the reader was blinded and assessed vertebral fracture, disc height narrowing, and facet joint OA on two separate occasions for 30 individuals. The correlation coefficients for intrareader reliability were 0.76 to 1.00 for vertebral fracture, 0.80 to 1.00 for disc height narrowing, and 0.73 to 1.00 for facet joint OA.

For each individual, we created a summary index for vertebral fracture, disc height narrowing, and facet joint OA, which takes into account the number of levels affected and severity at each level. We summed the SQ scores across all levels (13 levels for vertebral fracture and disc height narrowing, 26 levels (13 for right side and 13 for left side) for facet joint OA. The summary index ranged from 0 to 39 for vertebral fracture and disc height narrowing, and ranged from 0 to 78 for facet joint OA.

Vertebral fracture—The definition of fracture was based on Genant's SQ scale.[23] No fracture (SQ0) was defined as less than 20% reduction in any vertebral height, mild fracture (SQ1) as 20% to 25% reduction in any vertebral height, moderate fracture (SQ2) as 25% to 40% reduction, and severe fracture (SQ3) as more than 40% reduction.[23,24]

Disc height narrowing—We used Videman's approach to evaluate disc height narrowing.[25] No disc height narrowing (SQ0) was defined as a disc height greater than the height of the disc immediately superior, mild disc height narrowing (SQ1) as disc height equal to the height of disc immediately superior, moderate disc height narrowing (SQ2) as disc height less than the height of disc immediately superior, and severe disc height narrowing (SQ3) as vertebral endplates almost in contact.[25–27]

Facet joint OA—We graded facet joint OA bilaterally from T_4 to L_4 using a scale based on criteria described by Pathria and colleagues[28] and Weishaupt and colleagues.[29] No facet joint OA (SQ0) was defined as joint space ≥2 mm, mild degenerative disease (SQ1) as joint space <2 mm and/or small osteophytes and/or mild hypertrophy of the articular process, moderate degenerative disease (SQ2) as joint space <1 mm and/or moderate osteophytes and/or moderate hypertrophy of the articular process and/or mild subarticular bone erosions, and severe degenerative disease (SQ3) as no joint space and/or large osteophytes and/or severe hypertrophy of the articular process and/or severe subarticular bone erosions and/or subchondral cysts and/or vacuum phenomenon in the joints.[30–32]

vBMD

We measured integral vBMD (g/cm^3) at L_3 from reconstructed abdominal baseline CT scans acquired in 2002–2005 in combination with lateral scout views using previously published software developed by Lang and colleagues.[33,34] This was the only spine trait not measured on CT scans acquired in 2008–2011. Interreader and intrareader reliability were based on readings from two trained readers who analyzed scans from 16 participants, repeating measurements on the same set of scans within a minimum of 2 weeks apart. Interreader and intrareader correlation coefficients were greater than 0.85.[21]

Paraspinal muscle area and density

We measured muscle size and attenuation for the paraspinal muscles at the T_7 and T_8 vertebral levels, including the transversospinalis and erector spinae.[35] We spatially filtered each CT scan using a sigma filter to reduce noise while preserving edges and contoured each muscle at the mid-vertebral slice using an established image processing program (Analyze; Biomedical Imaging Resource, Mayo Clinic, Rochester, MN, USA).[36] Muscle size was calculated as the cross-sectional area (CSA; mm^2) within the muscle contour using a similar method previously used by Keller and colleagues.[37] Muscle density was calculated as the mean voxel attenuation within the muscle, an area-weighted average of the right and left sides (Hounsfield units [HU]). We standardized the measurement of muscle density based on a hydroxyapatite phantom (Image Analysis, Inc., Lexington, KY, USA) that was scanned with each participant. Voxels outside the range of −50 to 150 HU were excluded before calculation of cross-sectional area and density to remove voxels of pure fat or bone. Paraspinal muscle CSA and density were calculated as an area-weighted average of measurements at the transversospinalis and erector spinae. Measures at T_7 and T_8 vertebrae levels were averaged to obtain a single analysis variable for paraspinal muscle CSA and density.

Interreader and intrareader reliability was based on readings from two trained readers who analyzed scans from 16 participants, repeating measurements on the same set of scans within a minimum of 2 weeks apart. The interreader correlation coefficients were 0.96 to 0.98 for paraspinal muscle area and 0.98 to 0.99 for paraspinal muscle density. Intrareader correlation coefficients were 0.99 for paraspinal muscle area and 0.99 to 1.00 for paraspinal muscle density.

Covariates

We used information on age, weight, height, smoking, alcohol consumption, and physical activity assessed by clinical examination or questionnaires administered at study visits (cycle 8 in 2005–2008 for the second generation cohort, cycle 2 in 2008–2011 for the third generation cohort) at, or closest in time, to the CT acquisition. Weight was measured to the nearest 0.5 pound using a balance beam scale and height to the nearest 0.25 inch using a stadiometer. We calculated BMI by dividing weight (kg) by height squared (m^2). We defined participants as current smokers if they reported smoking at least one cigarette per day within the past year. Alcohol consumption (ounces per week) was determined by multiplying the average amount of alcohol in a single drink of beer, wine, or spirit by the average number of self-reported drinks per week. Physical activity level was assessed using the physical activity index (unitless), which is based on the average number of hours per day reported by participants performing sedentary, slight, moderate, and heavy levels of physical activity during work and leisure time.[38]

If information on weight ($n = 5$), height ($n = 7$), BMI ($n = 7$), smoking status ($n = 5$), alcohol consumption ($n = 348$), or physical activity index ($n = 22$) was missing, then values from the previous exam (2005–2008) were used. In rare cases where values for alcohol consumption from 2005–2008 were missing ($n = 3$), we used measures from 1995–1998.

Statistical methods

We used a variance components method to estimate genetic heritability $\left(h^2=\sigma_a^2/\sigma_p^2\right)$ for each spine trait. This approach partitions the phenotypic variation $\left(\sigma_p^2\right)$ into additive genetic $\left(\sigma_a^2\right)$ and environmental $\left(\sigma_c^2\right)$ components based on the observed covariance in the trait among family members $\left(\Omega=2\Phi\sigma_a^2+I\sigma_c^2\right)$, where 2Φ is the coefficient of relationship estimated from the pedigree and I is an identity matrix.[39,40]

We used bivariate models to quantify the amount of shared phenotypic variation that can be attributed to either shared genetic or environmental determinants. We estimated genetic correlations (ρ_G) and environmental correlations (ρ_E) between kyphosis angle and each spine trait based on $\rho_P=\rho_G\sqrt{h_1^2h_2^2}+\rho_E\sqrt{\left(1-h_1^2\right)\left(1-h_2^2\right)}$, where ρ_P is the phenotypic correlation between traits, and h_1^2 and h_2^2 are the heritability estimates for trait 1 and trait 2, respectively.[41] Heritability estimates, genetic correlations, and environmental correlations were adjusted for age, sex, and weight. We repeated the analysis with additional adjustment for current and previous height, BMI, smoking, physical activity, and alcohol

consumption. Further, we included an age^2 term to evaluate a potential nonlinear effect of age. However, results were unchanged, so we provided results for the parsimonious model. We considered each trait as an independent feature related to kyphosis biology. We therefore set the threshold for statistical significance at $\alpha = 0.05$. Analyses were conducted using SOLAR (San Antonio, TX, USA).[42]

Results

This study included 2063 individuals, 1011 women and 1052 men (Table 1). There were 870 participants in the second generation cohort and 1193 participants in the third generation cohort. The study sample included 578 families with mean size 4 ± 6 members (range, 1 to 95 members). There were 194 families that included second and third generation participants, 182 families that included second generation participants only, and 202 families that included third generation participants only. Mean age was 59 ± 11 years and ranged from 37 to 90 years. Mean kyphosis angle was 34.0 ± 9.6 degrees (range, 1.0 to 70.6 degrees) and increased with age (Fig. 2).

We estimated the unadjusted heritability of kyphosis angle to be 0.41 (95% CI, 0.30 to 0.51) (Table 2). After adjustment for age, sex, and weight, the heritability estimate increased to 0.54 (95% CI, 0.43 to 0.64). Adjusted heritability was highest for facet joint OA (h^2, 0.63; 95% CI, 0.47 to 0.79), followed by paraspinal muscle area (h^2, 0.54; 95% CI, 0.32 to 0.75) and disc height narrowing (h^2, 0.49; 95% CI, 0.31 to 0.66). Vertebral fracture (h^2, 0.41; 95% CI, 0.23 to 0.59) and vBMD (h^2, 0.40; 95% CI, 0.28 to 0.52) had similar estimates of heritability. Of the spine traits examined, paraspinal muscle density had the lowest adjusted heritability (h^2, 0.35; 95% CI, 0.16 to 0.55).

Genetic correlations were moderate between kyphosis angle and paraspinal muscle area ($\hat{\rho}_G$, −0.46; 95% CI, −0.67 to −0.26), vertebral fracture ($\hat{\rho}_G$, 0.39; 95% CI, 0.18 to 0.61), and vBMD ($\hat{\rho}_G$,−0.23; 95% CI, −0.41 to −0.04). Genetic correlations between kyphosis angle and paraspinal muscle density ($\hat{\rho}_G$,−0.22; 95% CI, −0.48 to 0.03) and disc height narrowing ($\hat{\rho}_G$, 0.17; 95% CI, −0.05 to 0.38) were smaller. Genetic correlation of kyphosis angle with facet joint OA was weakest among the traits considered ($\hat{\rho}_G$, 0.05; 95% CI, −0.15 to 0.24).

Environmental correlation between kyphosis angle and facet joint OA was strongest among all traits considered ($\hat{\rho}_E$, 0.28; 95% CI, 0.05 to 0.51). Environmental correlations between kyphosis angle and vertebral fracture, disc height narrowing, vBMD, paraspinal muscle density and area were low $(-0.20<\hat{\rho}_E<0.20; p>0.05)$.

Discussion

This study has two main findings that advance our understanding of the determinants of forward thoracic spine curvature. First, we found strong evidence of the influence of heredity on kyphosis. Specifically, we found that 54% (95% CI, 43% to 64%) of the variation in thoracic spine curvature (as measured by the kyphosis, or Cobb angle) in older adults is under genetic control. The only other report of heritability of thoracic spine

curvature is a twin study, which reported an estimate of 61% (95% CI, 46% to 72%). This was higher than our estimate of 54% (95% CI, 43% to 64%) based on extended families in a community-based cohort including both women and men. Twin studies may potentially overestimate heritability due to strong sharing of environmental factors between twins.[15,43] A second important finding from our study is that genetic determinants of thoracic spine curvature may also be responsible for decline in thoracic spine muscle size, loss of vertebral bone density, and increased prevalence of vertebral fracture. Genetic correlations between traits may reflect biological and functional interactions at the gene level.

Our finding of a moderate genetic correlation, −0.46 (95% CI, −0.67 to −0.26), between kyphosis angle and paraspinal muscle area is consistent with other studies showing genetic correlations ranging from 0.28 to 0.69 between different measures of muscle size and skeletal traits, including bone size, both in humans and animal models.[44] Muscle size in the lower extremities has been shown to have an effect on muscle strength and physical function.[45–47] The same may be true for the thoracic spine, where larger muscle size may be an indicator of increased muscle strength and capacity to stabilize the spine, which would decrease the risk of excessive thoracic spine curvature.

Although we found a shared hereditary component between thoracic spine curvature and muscle size, we found little genetic correlation between thoracic spine curvature and muscle density. Further, we found the environmental correlation between thoracic spine curvature and muscle density was two times larger than the environmental correlation between kyphosis angle and muscle area. This suggests that the shared determinants between thoracic spine curvature and muscle size are more likely to be genetic, whereas the shared determinants between thoracic spine curvature and muscle density may be mostly nongenetic in nature. Environmental factors, such as strength training, can decrease fatty infiltration (increase density) in the muscle without changing the size (area) of the muscle, as shown in intervention studies of resistance training in elders.[48] Regular physical activity may prevent loss of muscle strength and increase muscle density in older adults,[49] and there is some evidence that exercise may improve hyperkyphosis.[14]

We found that the genetic determinants of thoracic curvature may also be responsible for loss of vertebral bone density and increased prevalence of vertebral fracture. The Study of Osteoporotic Fractures (SOF) showed that vertebral fracture and low bone density, but not degenerative disc disease, independently increase severity of kyphosis as well as progression of kyphosis.[9] In particular, thoracic spine fractures are more strongly associated with kyphosis than lumbar spine fractures.[50] Biomechanical models of stress on the spine have suggested that vertebral wedging may increase as BMD decreases, leading to greater kyphosis.[51] As a result, vertebral fractures and lower vBMD may confer reduced structural integrity within the spinal column, decreasing the capacity of the spine to withstand load, leading to greater kyphosis.

We found little evidence for a shared genetic predisposition between kyphosis and intervertebral disc degeneration. In addition to the vertebral bodies, the intervertebral discs are the major contributors to the length and shape of the spinal column. Degenerative disc disease, particularly anterior disc height loss, has been associated with increased severity of

kyphosis in several studies.[9,52,53] Although disc degeneration may increase risk of kyphosis, low genetic correlation between kyphosis and disc degeneration suggests there may be few shared molecular mechanisms. This is supported by results from SOF, showing vertebral fracture and decreased BMD, but not disc degeneration, predicts kyphosis progression over 15 years independently of other risk factors.[9]

We found little evidence of genetic correlation, but did observe moderate environmental correlation, between kyphosis and facet joint OA. Because the facet joints and intervertebral discs are part of the same spinal "motion segment," facet joint OA is often observed in concert with degenerative disc disease.[54] Several studies have shown that degenerative changes in the intervertebral discs may occur at an earlier age and precede development of facet joint OA.[55–57] Our results imply that neither disc degeneration nor facet joint OA share genetic contributions to kyphosis. However, both kyphosis and facet joint OA have been associated with lower paraspinal muscle density.[11,58,59] Thus, the environmental correlation between kyphosis and facet joint OA that we observed may be due to common environmental factors, such as exercise, that can increase muscle density and confer protection against kyphosis and facet joint OA.

This is the first study to comprehensively consider together the structural components of the spine, including the vertebral bodies, intervertebral discs, facet joints, and spinal muscle. Further, we used state-of-the-art quantitative CT to evaluate spine traits, based on standardized, validated measures with high reliability. A summary index was used to represent the severity and number of affected spinal levels providing an overall burden of vertebral fracture, disc height narrowing, and facet joint OA for both the thoracic and lumbar spine. Although vertebral fracture and disc height narrowing have been previously evaluated in studies of hyperkyphosis, this is the first investigation to include facet joint OA. Finally, we evaluated a comprehensive set of potential confounders that were ascertained by comprehensive clinical examinations.

Our study has limitations that warrant consideration in the interpretation of results. Evaluation of vBMD was conducted 6 years prior to the other assessments, and vBMD was missing in 4% of the sample. As a result, we may have underestimated phenotypic, genotypic, and environmental correlations for vBMD. However, the overall distribution of vBMD was unlikely to have differed between study visits or with or without the missing data, so that estimates of heritability were not likely to have been affected. Also, the largely European ancestry of the Framingham Study restricts the ability to apply our findings to other race and ethnic groups.[60,61]

A final concern is that collider bias and multiple testing may have affected our results. Adjustment for strongly heritable traits, such as weight, may have introduced collider bias, thereby overestimating heritability and genetic correlations.[62] However, phenotypic and genotypic correlations between kyphosis angle and weight were small. As a result, collider bias was not likely to have had a strong effect on our estimates. We evaluated associations between kyphosis angle and six spine traits, so it is possible that multiple testing may have resulted in false-positive findings. We considered each of the six spine traits tested (vBMD, vertebral fracture, disc height narrowing, facet joint OA, muscle density, and muscle area) as

independent traits related to thoracic spine curvature. However, it is possible that underlying mechanisms that link these spine traits to thoracic spine curvature may be correlated. Applying a conservative Bonferroni correction to adjust for six non-independent tests would lower the threshold for statistical significance to $\alpha = 0.05/6 = 0.01$. Under this more stringent threshold, all tests that met statistical significance at the less stringent α level would remain statistically significant with the exception of genetic correlation between thoracic spine curvature and vBMD.

In conclusion, we found that severity of thoracic spine curvature is heritable and may share genetic factors involved in age-related bone and muscle loss. Better understanding of the molecular processes underlying shared genetic variation among spine traits may provide biological insights into the etiology of hyperkyphosis and related spine conditions.

Acknowledgments

This study was supported by the NIH (National Institute on Aging [NIA], R01AG041658; National Heart Lung and Blood Institute [NHLBI] Framingham Heart Study, Contract No. HHSN268201500001I); MSY is supported by NIH (NIA T32AG023480) and Friends of Hebrew SeniorLife; DK is supported by ISF Grant No. 1283/14.

Authors' roles: Study concept and design: DPK, MLB, DK, and EJS. Data collection: DEA, ALL, BTA, LY, MLB, and EJS. Data analysis and interpretation: MSY, SD, YZ, LAC, TGT, DK, and EJS. Drafting manuscript: MSY, DK, and EJS. Critical review and final approval of manuscript content: MSY, SD, YZ, DEA, ALL, DPK, BTA, LY, LAC, TGT, MLB, DK, and EJS. MSY and EJS take responsibility for the integrity of the data and accuracy of the data analyses.

References

1. Kado DM, Prenovost K, Crandall C. Narrative review: hyperkyphosis in older persons. Ann Intern Med. 2007; 147(5):330–8. [PubMed: 17785488]
2. Kado DM, Lui LY, Ensrud KE, et al. Hyperkyphosis predicts mortality independent of vertebral osteoporosis in older women. Ann Intern Med. 2009; 150(10):681–7. [PubMed: 19451575]
3. Kado DM, Huang MH, Barrett-Connor E, Greendale GA. Hyperkyphotic posture and poor physical functional ability in older community-dwelling men and women: the Rancho Bernardo study. J Gerontol A Biol Sci Med Sci. 2005; 60(5):633–7. [PubMed: 15972617]
4. Katzman WB, Huang MH, Lane NE, Ensrud KE, Kado DM. Kyphosis and decline in physical function over 15 years in older community-dwelling women: the Study of Osteoporotic Fractures. J Gerontol A Biol Sci Med Sci. 2013; 68(8):976–83. [PubMed: 23633167]
5. Katzman WB, Harrison SL, Fink HA, et al. Physical function in older men with hyperkyphosis. J Gerontol A Biol Sci Med Sci. 2015; 70(5):635–40. [PubMed: 25431353]
6. Katzman WB, Vittinghoff E, Ensrud K, Black DM, Kado DM. Increasing kyphosis predicts worsening mobility in older community-dwelling women: a prospective cohort study. J Am Geriatr Soc. 2011; 59(1):96–100. [PubMed: 21198460]
7. Kado DM, Huang MH, Nguyen CB, Barrett-Connor E, Greendale GA. Hyperkyphotic posture and risk of injurious falls in older persons: the Rancho Bernardo Study. J Gerontol A Biol Sci Med Sci. 2007; 62(6):652–7. [PubMed: 17595423]
8. Renno AC, Silveira Gomes AR, Nascimento RB, Salvini T, Parizoto N. Effects of a progressive loading exercise program on the bone and skeletal muscle properties of female osteopenic rats. Exp Gerontol. 2007; 42(6):517–22. [PubMed: 17196352]
9. Kado DM, Huang MH, Karlamangla AS, et al. Factors associated with kyphosis progression in older women: 15 years' experience in the study of osteoporotic fractures. J Bone Miner Res. 2013; 28(1): 179–87. [PubMed: 22865329]
10. Schneider DL, von Muhlen D, Barrett-Connor E, Sartoris DJ. Kyphosis does not equal vertebral fractures: the Rancho Bernardo study. J Rheumatol. 2004; 31(4):747–52. [PubMed: 15088302]

11. Katzman W, Cawthon P, Hicks GE, et al. Association of spinal muscle composition and prevalence of hyperkyphosis in healthy community-dwelling older men and women. J Gerontol A Biol Sci Med Sci. 2012; 67(2):191–5. [PubMed: 21878482]
12. Katzman WB, Miller-Martinez D, Marshall LM, Lane NE, Kado DM. Kyphosis and paraspinal muscle composition in older men: a cross-sectional study for the Osteoporotic Fractures in Men (MrOS) research group. BMC Musculoskelet Disord. 2014; 15:19. [PubMed: 24428860]
13. Katzman WB, Wanek L, Shepherd JA, Sellmeyer DE. Age-related hyperkyphosis: its causes, consequences, and management. J Orthop Sports Phys Ther. 2010; 40(6):352–60. [PubMed: 20511692]
14. Bansal S, Katzman WB, Giangregorio LM. Exercise for improving age-related hyperkyphotic posture: a systematic review. Arch Phys Med Rehabil. 2014; 95(1):129–40. [PubMed: 23850611]
15. Stone MA, Osei-Bordom DC, Inman RD, Sammon C, Wolber LE, Williams FM. Heritability of spinal curvature and its relationship to disc degeneration and bone mineral density in female adult twins. Eur Spine J. 2015; 24(11):2387–94. [PubMed: 25070789]
16. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The Framingham Offspring Study. Design and preliminary data. Prev Med. 1975; 4(4):518–25. [PubMed: 1208363]
17. Splansky GL, Corey D, Yang Q, et al. The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. Am J Epidemiol. 2007; 165(11):1328–35. [PubMed: 17372189]
18. Moselewski F, O'Donnell CJ, Achenbach S, et al. Calcium concentration of individual coronary calcified plaques as measured by multidetector row computed tomography. Circulation. 2005; 111(24):3236–41. [PubMed: 15956133]
19. Hoffmann U, Siebert U, Bull-Stewart A, et al. Evidence for lower variability of coronary artery calcium mineral mass measurements by multi-detector computed tomography in a community-based cohort—consequences for progression studies. Eur J Radiol. 2006; 57(3):396–402. [PubMed: 16434160]
20. Parikh NI, Hwang SJ, Larson MG, et al. Parental occurrence of premature cardiovascular disease predicts increased coronary artery and abdominal aortic calcification in the Framingham Offspring and Third Generation cohorts. Circulation. 2007; 116(13):1473–81. [PubMed: 17785619]
21. Samelson EJ, Christiansen BA, Demissie S, et al. QCT measures of bone strength at the thoracic and lumbar spine: the Framingham Study. J Bone Miner Res. 2012; 27(3):654–63. [PubMed: 22143959]
22. Kim YM, Demissie S, Eisenberg R, Samelson EJ, Kiel DP, Bouxsein ML. Intra-and inter-reader reliability of semi-automated quantitative morphometry measurements and vertebral fracture assessment using lateral scout views from computed tomography. Osteoporos Int. 2011; 22(10): 2677–88. [PubMed: 21271340]
23. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res. 1993; 8(9):1137–48. [PubMed: 8237484]
24. Samelson EJ, Christiansen BA, Demissie S, et al. Reliability of vertebral fracture assessment using multidetector CT lateral scout views: the Framingham Osteoporosis Study. Osteoporos Int. 2011; 22(4):1123–31. [PubMed: 20495902]
25. Videman T, Battie MC, Ripatti S, Gill K, Manninen H, Kaprio J. Determinants of the progression in lumbar degeneration: a 5-year follow-up study of adult male monozygotic twins. Spine (Phila Pa 1976). 2006; 31(6):671–8. [PubMed: 16540872]
26. Raininko R, Manninen H, Battie MC, Gibbons LE, Gill K, Fisher LD. Observer variability in the assessment of disc degeneration on magnetic resonance images of the lumbar and thoracic spine. Spine (Phila Pa 1976). 1995; 20(9):1029–35. [PubMed: 7631232]
27. Suri P, Hunter DJ, Rainville J, Guermazi A, Katz JN. Quantitative assessment of abdominal aortic calcification and associations with lumbar intervertebral disc height loss: the Framingham Study. Spine J. 2012; 12(4):315–23. [PubMed: 22561175]
28. Pathria M, Sartoris DJ, Resnick D. Osteoarthritis of the facet joints: accuracy of oblique radiographic assessment. Radiology. 1987; 164(1):227–30. [PubMed: 3588910]
29. Weishaupt D, Zanetti M, Boos N, Hodler J. MR imaging and CT in osteoarthritis of the lumbar facet joints. Skeletal Radiol. 1999; 28(4):215–9. [PubMed: 10384992]

30. Kalichman L, Li L, Kim DH, et al. Facet joint osteoarthritis and low back pain in the community-based population. Spine (Phila Pa 1976). 2008; 33(23):2560–5. [PubMed: 18923337]
31. Kalichman L, Suri P, Guermazi A, Li L, Hunter DJ. Facet orientation and tropism: associations with facet joint osteoarthritis and degeneratives. Spine (Phila Pa 1976). 2009; 34(16):E579–85. [PubMed: 19770601]
32. Suri P, Hunter DJ, Rainville J, Guermazi A, Katz JN. Presence and extent of severe facet joint osteoarthritis are associated with back pain in older adults. Osteoarthritis Cartilage. 2013; 21(9): 1199–206. [PubMed: 23973131]
33. Lang TF, Guglielmi G, van Kuijk C, De Serio A, Cammisa M, Genant HK. Measurement of bone mineral density at the spine and proximal femur by volumetric quantitative computed tomography and dual-energy X-ray absorptiometry in elderly women with and without vertebral fractures. Bone. 2002; 30(1):247–50. [PubMed: 11792593]
34. Lang T, LeBlanc A, Evans H, Lu Y, Genant H, Yu A. Cortical and trabecular bone mineral loss from the spine and hip in long-duration spaceflight. J Bone Miner Res. 2004; 19(6):1006–12. [PubMed: 15125798]
35. Anderson DE, D'Agostino JM, Bruno AG, Demissie S, Kiel DP, Bouxsein ML. Variations of CT-based trunk muscle attenuation by age, sex, and specific muscle. J Gerontol A Biol Sci Med Sci. 2013; 68(3):317–23. [PubMed: 22904095]
36. Robb RA. The biomedical imaging resource at Mayo Clinic. IEEE Trans Med Imaging. 2001; 20(9):854–67. [PubMed: 11585203]
37. Keller A, Gunderson R, Reikeras O, Brox JI. Reliability of computed tomography measurements of paraspinal muscle cross-sectional area and density in patients with chronic low back pain. Spine (Phila Pa 1976). 2003; 28(13):1455–60. [PubMed: 12838105]
38. Young DR, Sharp DS, Petrovitch H, Curb JD. Internal validity of the physical activity index over 26 years in middle-aged and older men. J Am Geriatr Soc. 1995; 43(9):999–1006. [PubMed: 7657940]
39. Amos CI. Robust variance-components approach for assessing genetic linkage in pedigrees. Am J Hum Genet. 1994; 54(3):535–43. [PubMed: 8116623]
40. Almasy L, Blangero J. Variance component methods for analysis of complex phenotypes. Cold Spring Harb Protoc. 2010 May.2010(5) pdb.top77. doi: 10.1101/pdb.top77
41. Falconer, DS., Mackay, TFC. Introduction to quantitative genetics. 4th. Essex, England: Longman; 1996. p. xiiip. 464
42. Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. Am J Hum Genet. 1998; 62(5):1198–211. [PubMed: 9545414]
43. Livshits G, Popham M, Malkin I, et al. Lumbar disc degeneration and genetic factors are the main risk factors for low back pain in women: the UK Twin Spine Study. Ann Rheum Dis. 2011; 70(10):1740–5. [PubMed: 21646416]
44. Karasik D, Kiel DP. Evidence for pleiotropic factors in genetics of the musculoskeletal system. Bone. 2010; 46(5):1226–37. [PubMed: 20149904]
45. Visser M, Kritchevsky SB, Goodpaster BH, et al. Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: the Health, Aging and Body Composition Study. J Am Geriatr Soc. 2002; 50(5):897–904. [PubMed: 12028178]
46. Visser M, Goodpaster BH, Kritchevsky SB, et al. Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. J Gerontol A Biol Sci Med Sci. 2005; 60(3):324–33. [PubMed: 15860469]
47. Delmonico MJ, Harris TB, Lee JS, et al. Alternative definitions of sarcopenia, lower extremity performance, and functional impairment with aging in older men and women. J Am Geriatr Soc. 2007; 55(5):769–74. [PubMed: 17493199]
48. Taaffe DR, Henwood TR, Nalls MA, Walker DG, Lang TF, Harris TB. Alterations in muscle attenuation following detraining and retraining in resistance-trained older adults. Gerontology. 2009; 55(2):217–23. [PubMed: 19060453]
49. Goodpaster BH, Chomentowski P, Ward BK, et al. Effects of physical activity on strength and skeletal muscle fat infiltration in older adults: a randomized controlled trial. J Appl Physiol (1985). 2008; 105(5):1498–503. [PubMed: 18818386]

50. Ensrud KE, Black DM, Harris F, Ettinger B, Cummings SR. Correlates of kyphosis in older women. The Fracture Intervention Trial Research Group. J Am Geriatr Soc. 1997; 45(6):682–7. [PubMed: 9180660]
51. Bouxsein ML, Melton LJ 3rd, Riggs BL, et al. Age- and sex-specific differences in the factor of risk for vertebral fracture: a population-based study using QCT. J Bone Miner Res. 2006; 21(9): 1475–82. [PubMed: 16939406]
52. Manns RA, Haddaway MJ, McCall IW, Cassar Pullicino V, Davie MW. The relative contribution of disc and vertebral morphometry to the angle of kyphosis in asymptomatic subjects. Clin Radiol. 1996; 51(4):258–62. [PubMed: 8617037]
53. Goh S, Price RI, Leedman PJ, Singer KP. The relative influence of vertebral body and intervertebral disc shape on thoracic kyphosis. Clin Biomech (Bristol, Avon). 1999; 14(7):439–48.
54. Gellhorn AC, Katz JN, Suri P. Osteoarthritis of the spine: the facet joints. Nat Rev Rheumatol. 2013; 9(4):216–24. [PubMed: 23147891]
55. Vernon-Roberts B, Pirie CJ. Degenerative changes in the intervertebral discs of the lumbar spine and their sequelae. Rheumatol Rehabil. 1977; 16(1):13–21. [PubMed: 847320]
56. Fujiwara A, Tamai K, Yamato M, et al. The relationship between facet joint osteoarthritis and disc degeneration of the lumbar spine: an MRI study. Eur Spine J. 1999; 8(5):396–401. [PubMed: 10552323]
57. Suri P, Miyakoshi A, Hunter DJ, et al. Does lumbar spinal degeneration begin with the anterior structures? A study of the observed epidemiology in a community-based population. BMC Musculoskelet Disord. 2011; 12:202. [PubMed: 21914197]
58. Kalichman L, Kim DH, Li L, Guermazi A, Hunter DJ. Computed tomography-evaluated features of spinal degeneration: prevalence, intercorrelation, and association with self-reported low back pain. Spine J. 2010; 10(3):200–8. [PubMed: 20006557]
59. Kalichman L, Hodges P, Li L, Guermazi A, Hunter DJ. Changes in paraspinal muscles and their association with low back pain and spinal degeneration: CT study. Eur Spine J. 2010; 19(7):1136–44. [PubMed: 20033739]
60. Tang H, Quertermous T, Rodriguez B, et al. Genetic structure, self-identified race/ethnicity, and confounding in case-control association studies. Am J Hum Genet. 2005; 76(2):268–75. [PubMed: 15625622]
61. Bryc K, Durand EY, Macpherson JM, Reich D, Mountain JL. The genetic ancestry of African Americans, Latinos, and European Americans across the United States. Am J Hum Genet. 2015; 96(1):37–53. [PubMed: 25529636]
62. Aschard H, Vilhjalmsson BJ, Joshi AD, Price AL, Kraft P. Adjusting for heritable covariates can bias effect estimates in genome-wide association studies. Am J Hum Genet. 2015; 96(2):329–39. [PubMed: 25640676]

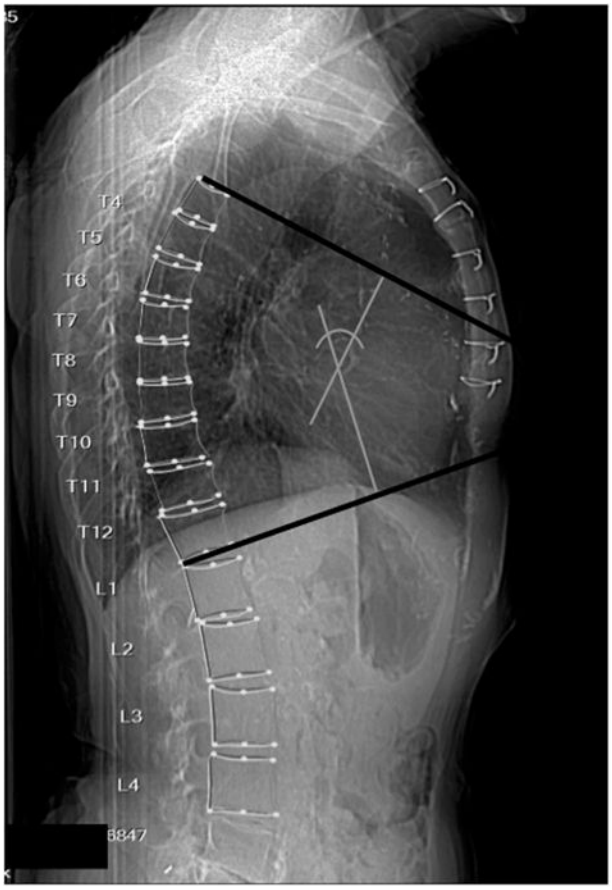

Fig. 1.
Illustration of semiautomated algorithm used to measure kyphosis (Cobb) angle (T_4–T_{12}) on CT scout images (SpineAnalyzer; Optasia Medical, Cheadle, UK).

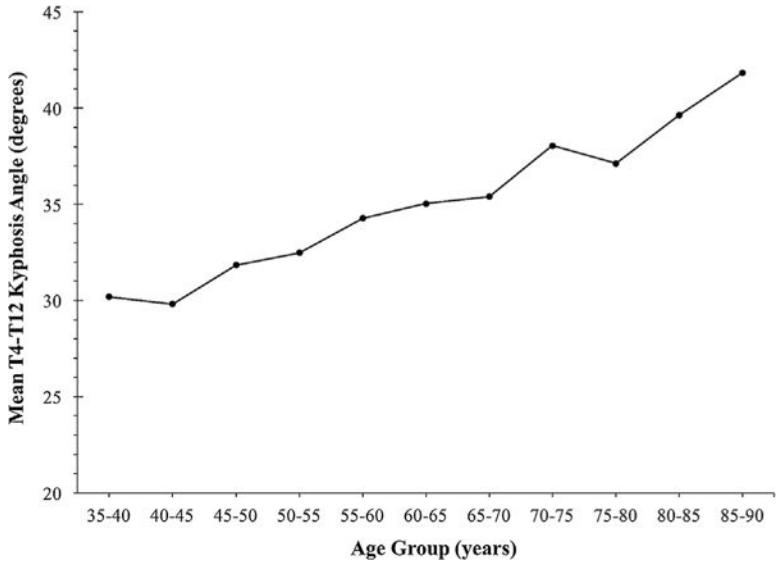

Fig. 2.

Distribution of kyphosis angle by age in the Framingham Study. Mean values of kyphosis angle (T_4–T_{12}, in degrees) are presented by 5-year age group.

Table 1

Cohort Characteristics (2008–2011)

	n	Total (*n* = 2063)	2nd Generation (*n* = 870)	3rd Generation (*n* = 1193)
Cobb kyphosis angle (degrees)	2063	34.0 ± 9.6	36.4 ± 10.1	32.2 ± 8.8
Clinical characteristics (units)				
Women (%)	2063	49	55	48
Age (years)	2063	59 ± 11	69 ± 9	51 ± 6
Weight (lbs)[a]	2063	180 ± 39	176 ± 37	184 ± 41
Height (in)[a]	2063	67 ± 4	66 ± 4	67 ± 4
BMI (kg/m^2)[a]	2063	28 ± 5	28 ± 5	29 ± 5
Current smoker (%)	2063	7	6	8
Former smoker (%)	2063	44	55	36
Never smoker (%)	2063	49	40	57
Alcohol consumption (ounces/week)[a]	2063	2 ± 4	2 ± 4	3 ± 3
Physical activity index[a]	2063	36 ± 7	36 ± 5	36 ± 7
Spine traits (units)				
Vertebral fracture (summary index)[b]	1172	1 ± 2	1 ± 2	0 ± 1
Disc height narrowing (summary index)[b]	1172	9 ± 6	9 ± 6	7 ± 6
Facet joint OA (summary index)[b]	1172	26 ± 13	28 ± 13	22 ± 11
L_3 Integral volumetric BMD (g/cm^3)[c]	1976	0.19 ± 0.04	0.17 ± 0.04	0.20 ± 0.03
T_7/T_8 Paraspinal muscle cross-sectional area (mm^2)[c]	1110	720.2 ± 190.9	703.4 ± 182.3	765.0 ± 205.9
T_7/T_8 Paraspinal muscle density (HU)[c]	1109	26.5 ± 12.2	25.2 ± 12.4	30.0 ± 10.7

Values are mean ± SD or % as indicated.

[a] In the second generation, there were 5 missing values for weight, 6 missing values for height, 6 missing values for BMI, 5 missing values for smoking, 342 missing values for alcohol consumption, and 10 missing values for physical activity index, which were imputed from measures taken in 2005–2008. There were 3 missing values for alcohol consumption that were imputed from measures taken in 1995–1998. In the third generation, there was 1 missing value for height, 1 missing value for BMI, 6 missing values for alcohol consumption, and 12 missing values for physical activity index, which were imputed with from measures taken in 2005–2008.

[b] Vertebral fracture, disc height narrowing, and facet joint OA were evaluated in 1172 individuals age 50 years and older. Summary indices were calculated by summing the grades at each level (13 levels for vertebral fracture and disc height narrowing, 26 levels for [right and left] facet joint OA); range, 0 to 39 for vertebral fracture and disc height narrowing; and range, 0 to 78 for facet joint OA.

[c] vBMD measured from CT scans acquired in 2005–2008. vBMD was missing in 87 individuals, paraspinal muscle cross-sectional area was missing in 62 individuals, and paraspinal muscle density was missing in 63 individuals.

Table 2

Heritability of Kyphosis Angle and Other Spine Traits and Phenotypic, Genetic, and Environmental Correlations Between Kyphosis Angle and Other Spine Traits

		Heritability		Adjusted correlations between kyphosis angle and other spine traits[a]					
	n	Crude h^2 (95% CI)	Adjusted h^2 (95% CI)[a]	$\hat{\rho}_P$ (95% CI)	*p*	$\hat{\rho}_G$ (95% CI)	*p*	$\hat{\rho}_E$ (95% CI)	*p*
Kyphosis angle (degrees)	2063	0.41 (0.30 to 0.51)[b]	0.54 (0.43 to 0.64)[b]	—	—	—	—	—	—
Vertebral fracture (summary index)	1192	0.39 (0.22 to 0.57)[b]	0.41 (0.23 to 0.59)[b]	0.27 (0.21 to 0.32)	<0.01	0.39 (0.18 to 0.61)	<0.01	0.15 (−0.04 to 0.34)	0.13
Disc height narrowing (summary index)	1191	0.49 (0.32 to 0.67)[b]	0.49 (0.31 to 0.66)[b]	0.15 (0.10 to 0.21)	<0.01	0.17 (−0.05 to 0.38)	0.14	0.14 (−0.07 to 0.35)	0.19
Facet joint OA (summary index)	1191	0.56 (0.40 to 0.72)[b]	0.63 (0.47 to 0.79)[b]	0.14 (0.09 to 0.20)	<0.01	0.05 (−0.15 to 0.24)	0.64	0.28 (0.05 to 0.51)	0.02
L_3 vBMD (g/cm^3)	2002	0.19 (0.08 to 0.29)[b]	0.40 (0.28 to 0.52)[b]	−0.07 (−0.12 to −0.03)	<0.01	−0.23 (−0.41 to −0.04)	0.02	0.06 (−0.09 to 0.21)	0.41
T_7/T_8 paraspinal muscle area (mm^2)	1123	0.37 (0.17 to 0.58)[b]	0.54 (0.32 to 0.75)[b]	−0.28 (−0.33 to −0.22)	<0.01	−0.46 (−0.67 to −0.26)	<0.01	−0.07 (−0.29 to 0.14)	0.51
T_7/T_8 paraspinal muscle density (HU)	1123	0.32 (0.11 to 0.52)[b]	0.35 (0.16 to 0.55)[b]	−0.19 (−0.24 to −0.13)	<0.01	−0.22 (−0.48 to 0.03)	0.10	−0.16 (−0.35 to 0.03)	0.11

[a] Adjusted for age, sex, and weight. Bivariate models were used to estimate genetic correlations (ρ_G) and environmental correlations (ρ_E) between kyphosis angle and each spine trait based on $\rho_P = \rho_G \sqrt{h_1^2 h_2^2} + \rho_E \sqrt{\left(1 - h_1^2\right)\left(1 - h_2^2\right)}$ where (ρ_P) is the phenotypic correlation between traits, and h_1^2 and h_2^2 are the heritability estimates for trait 1 and trait 2, respectively.[41]

[b] $p < 0.001$.